RESTITUTION OF ACTION POTENTIAL DURATION AT THE PURKINJE-VENTRICULAR INTERFACE

D. J. Huelsing
Department of Biomedical Engineering and Cardiac Rhythm Management Lab, University of Alabama at Birmingham, Birmingham, Alabama

Abstract-**Regional differences in the restitution of action potential duration may be arrhythmogenic. Though such a difference exists at the Purkinje-ventricular interface, restitution kinetics have not yet been defined between coupled Purkinje and ventricular cells. Thus, the purpose of this study was to determine the effects of coupling on restitution in Purkinje and ventricular cells. DiFrancesco-Noble and Luo-Rudy dynamic membrane equations were used to describe the ionic currents for Purkinje and ventricular cells, respectively. During homogeneous coupling (e.g., Purkinje to Purkinje cell or ventricular to ventricular cell), the restitution kinetics of well-coupled cells were intermediate to the intrinsic restitution kinetics of each cells. However, during heterogeneous coupling between a Purkinje and a ventricular cell, the restitution kinetics of the coupled cells were not simply a weighted average of the intrinsic kinetics. These results suggest that restitution is strongly affected by cell-to-cell coupling. Because Purkinje and ventricular cells have intrinsic differences in restitution that are differentially altered by many pharmacological agents, these results have implications for proarrhythmic effects of some antiarrhythmic drugs.**

Keywords **- DiFrancesco-Noble, Luo-Rudy dynamic membrane equations**

I. INTRODUCTION

Purkinje and ventricular myocytes are electrically isolated from each other except at Purkinje-ventricular junctions. At these junctions, electrotonic interactions between Purkinje and ventricular cells modulate repolarization [1]. We previously showed that during electrical coupling between isolated rabbit Purkinje and ventricular myocytes, the action potential durations of both cells shortened upon coupling [2]. This was in contrast to homogeneous (Purkinje-to-Purkinje or ventricular-to-ventricular) coupling, which demonstrated shortening of the intrinsically longer action potential and prolongation of the intrinsically shorter action potential. The purpose of this study was to determine how action potential duration restitution was affected during coupling.

II. METHODOLOGY

The DiFrancesco-Noble [3] and Luo-Rudy dynamic [4,5] membrane equations were used to describe the ionic currents for Purkinje and ventricular cells, respectively. Action potentials were calculated by numerically solving the equations:

$$\frac{V_{m,v} - V_{m,p}}{R_j} = S_m\left(C_m \frac{dV_{m,p}}{dt} + I_{ion,p}\right) \quad (1)$$

$$\frac{V_{m,v} - V_{m,p}}{R_j} = S_m\left(C_m \frac{dV_{m,p}}{dt} + I_{ion,p}\right) \quad (2)$$

where $V_{m,v}$ and $V_{m,p}$ are the transmembrane potentials of the ventricular and Purkinje cells, respectively; S_m is the membrane surface area; C_m is the membrane capacitance; R_j is the junctional resistance between cells; and $I_{ion,v}$ and $I_{ion,p}$ are the total ionic currents of the ventricular and Purkinje cells, respectively. All simulations were performed on a Sun Microsystems SPARC4 workstation.

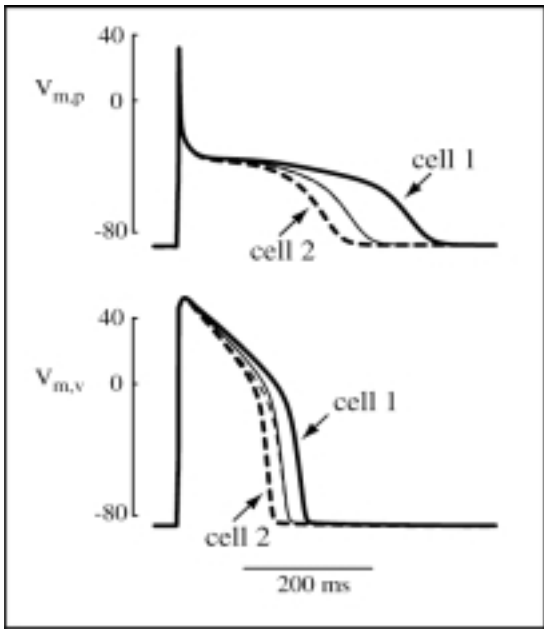

Fig. 1. Purkinje (top) and ventricular (bottom) action potentials. Thick traces show intrinsic action potentials, and thin traces show coupled action potentials that are intermediate to intrinsic action potentials.

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Abstract

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For simulations in which homogeneous coupling between two Purkinje cells or two ventricular cells was modeled, the delayed rectifier current was doubled in cell 2 to yield a shorter action potential. Fig. 1 shows Purkinje (top) and ventricular (bottom) action potentials. For each cell pair, cell 1 (thick solid trace) had a longer intrinsic action potential duration than cell 2 (thick dashed trace), where action potential duration was defined as the time of 90% repolarization. During homogeneous coupling between Purkinje cells or between ventricular cells, the coupled action potentials were intermediate to the intrinsic action potentials.

Restitution curves were generated for intrinsic action potentials and during homogeneous and heterogeneous coupling. Before the restitution protocol was initiated, the cells were paced to steady-state at a basic cycle length of 1 s for 100 "priming" beats. To determine restitution kinetics, premature stimuli were introduced every tenth beat after progressively longer diastolic intervals (DIs). Restitution curves were then generated by plotting action potential duration of the premature test beat (APDt) against the preceding DI, and kinetics were derived from exponential curve fits using KaleidaGraph 3.5 software (Synergy Software, Reading, PA).

III. Results

A. Restitution during coupling between two Purkinje cells

The priming simulations established basic action potential durations (APDb) for the uncoupled Purkinje cells of 374 ms and 241 ms. The first premature stimulus was timed to yield a 25 ms DI after the last basic action potential. This resulted in an APDt of 208 ms for cell 1 (with the intrinsically longer action potential) and 129 ms for cell 2 (with the intrinsically shorter action potential). Ten more action potentials were subsequently initiated at the basic cycle length of 1 s before another premature stimulus was applied after a longer DI. Longer DIs established longer test durations. Fig. 2 shows the restitution curves for these two uncoupled Purkinje cells. The kinetics of restitution were defined by fitting the curves to the following double exponential relation:

$$APD_t = APD_m \cdot \left[1 - \left(A_1 \cdot \exp(-t/\tau_1)\right) - \left(A_2 \cdot \exp(-t/\tau_2)\right)\right] \quad (3)$$

where APD_m was the asymptotic value of APD_t; τ_1 and τ_2 were the time constants of the exponential components; and A_1 and A_2 were their respective amplitudes. The restitution kinetics for the intrinsically longer Purkinje action potential were equally weighted between the fast and slow exponential components (A_1 = 0.326, τ_1 = 347, A_2 = 0.323, τ_2 = 3448), while those for the intrinsically shorter Purkinje action potential demonstrated a greater weighting toward the fast time component (A_1 = 0.428, τ_1 = 372, A_2 = 0.179, τ_2 = 3579). The asymptotic values for the uncoupled Purkinje cells were 560 ms for the long action potential and 305 ms for the short action potential.

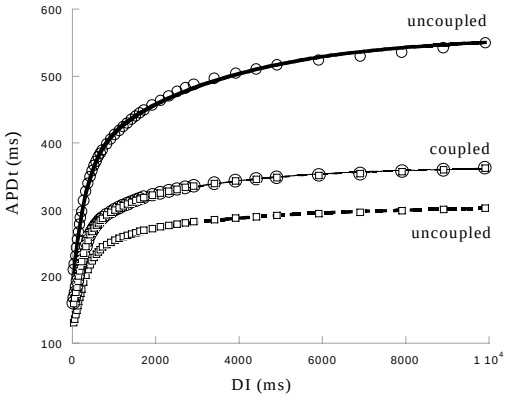

Fig. 2. Intrintsic and coupled Purkinje restitution curves.

When cells were coupled at steady-state, the coupled action potentials had durations that were closer to those of the intrinsically shorter action potential (see Fig. 1). Consistent with that steady-state behavior, the restitution curves for coupled cells also were closer to the restitution curve of the cell with the intrinsically shorter action potential.

When two Purkinje cells of different "sizes" were coupled, the restitution curves were weighted towards the intrinsic curve of the larger cell. Fig. 3 shows the intrinsic and coupled restitution curves for cells of unequal size. The coupled restitution curves shifted upward when the size of the cell with the longer action potential was doubled.

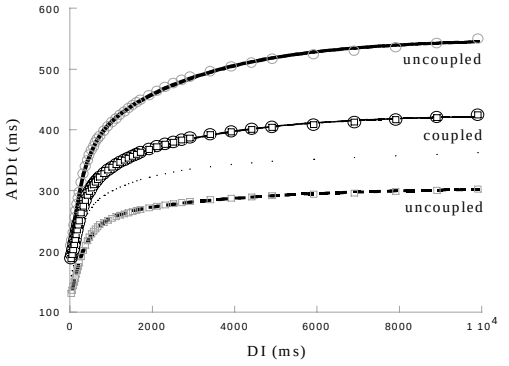

Fig. 3. Intrintsic and coupled Purkinje restitution curves for 2 cells of unequal size.

B. *Restitution during coupling between two ventricular cells*

Similarly, the two ventricular cells demonstrated intrinsically different restitution characteristics and nearly identical kinetics during coupling at R_j = 50 MΩ. Table 1 summarizes the restitution kinetics during homogeneous coupling for the ventricular cells.

TABLE I
Ventricular restitution kinetics during homogeneous coupling

	uncoupled		coupled	
	Cell 1	Cell 2	Cell 1	Cell 2
APD_m	205	151	181	180
A_1	0.392	0.448	0.42	0.42
τ_1	117	113	113	113
A_2	0.064	0.054	0.057	0.055
τ_2	6109	5765	5508	4902

The restitution curves were better fit by double exponentials (R = 0.999) than single exponentials (R = 0.89), though the amplitude of the slow τ_2 components was much smaller for the intrinsic and coupled ventricular cells than for the Purkinje cells.

C. Restitution during Purkinje-ventricular coupling

Fig. 4 demonstrates that during steady-state coupling of Purkinje and ventricular cells, the coupled action potential durations were not intermediate to the intrinsic durations.

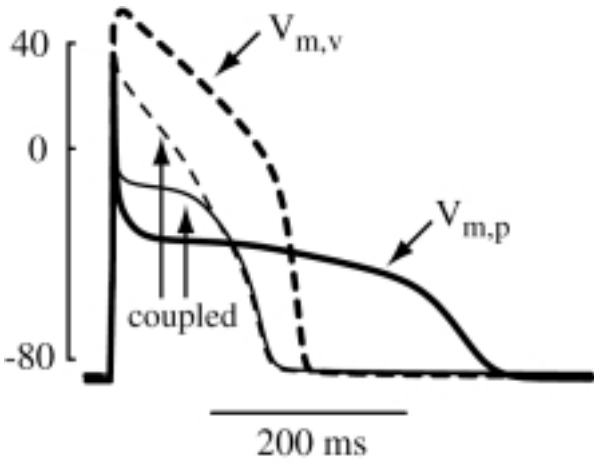

Fig. 4. Intrinsic and coupled (R_j = 50 MΩ) Purkinje and ventricular action potentials.

As previously demonstrated in single rabbit myocytes, the coupled Purkinje and ventricular action potentials were shorter than both intrinsic action potentials [2]. Rabbit Purkinje myocytes demonstrate a much larger degree of phase 1 repolarization than ventricular myocytes, and this difference in membrane potentials during the plateau induces the following series of events: First, a large electrotonic current severely depresses the ventricular plateau and raises the Purkinje plateau. Second, the hyperpolarization of the ventricular plateau contributes to voltage-dependent inactivation of the L-type calcium current and early activation of the inward rectifier current. These events contribute to accelerated repolarization of the ventricular cell. Finally, the mismatch in membrane resistance between the Purkinje and ventricular cells dictates an accelerated repolarization of the Purkinje cell as well [2].

Fig. 5 shows the restitution curves generated before and after coupling of the Purkinje and ventricular cells. The uncoupled Purkinje cell demonstrated a much steeper restitution relation than the uncoupled ventricular cell. During coupling at very short diastolic intervals (< 120 ms), the coupled Purkinje and ventricular action potential durations were intermediate to their intrinsic action potential durations. This was in contrast to shortening of both action potentials observed during steady-state coupling (Fig. 4). However, during coupling at diastolic intervals greater than 120 ms, the coupled Purkinje and ventricular action potentials were shorter than both intrinsic action potential durations.

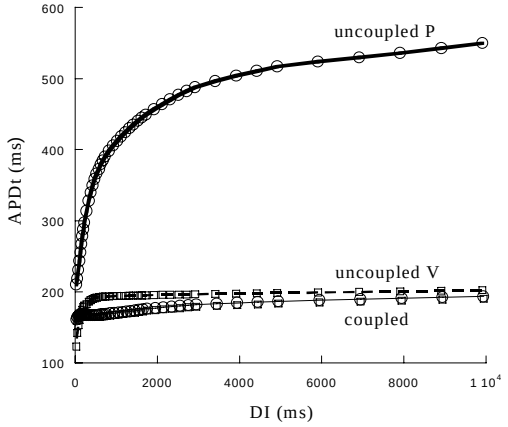

Fig. 5. Restitution curves for uncoupled Purkinje and ventricular cells and during coupling of Purkinje and ventricular cells.

Because the density of transient outward current in the Purkinje cells strongly influenced action potential duration during steady-state coupling [2], I hypothesized that inhibition of transient outward current would cause the restitution curves during coupling to fall between the intrinsic restitution curves. Fig. 6 shows restitution curves during such inhibition.

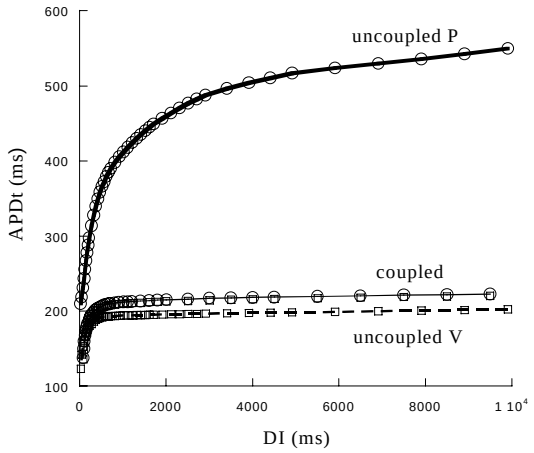

Fig. 6. Restitution curves for a 30-fold reduction of transient outward current in the Purkinje cell.

Consistent with that hypothesis, the coupled Purkinje and ventricular action potential durations were intermediate to the intrinsic durations for all diastolic intervals. Inhibition of transient outward current reduced the voltage gradient between the Purkinje and ventricular cell during the early action potential plateau. Subsequent electrotonic interactions promoted action potential prolongation in the ventricular cell and shortening in the Purkinje cell, relative to intrinsic action potential durations.

IV. Discussion

Restitution has been well-defined in preparations with homogeneous membrane properties, such as ventricular sheets, Purkinje fibers, and isolated myocytes. At the interface between different cell types (e.g., the Purkinje-ventricular junction), there exists a heterogeneity of restitution that may serve to predispose the tissue to unidirectional block of premature stimuli.

In the present study, homogeneous coupling resulted in a gradation of restitution such that the restitution curves of coupled cells were intermediate to the intrinsic curves. For equally sized cells, coupled restitution curves were weighted toward that of the intrinsically shorter action potential duration. Increasing cell mass resulted in a shift of the restitution curve toward that of the larger cell. The membrane resistance, which is inversely related to cell size, importantly affects electrotonic interactions by dictating the change in voltage that will occur for a given current magnitude.

During heterogeneous coupling between the standard Purkinje and ventricular cells, the coupled restitution curves were intermediate to the intrinsic curves only at very short diastolic intervals. At these intervals, transient outward current had not sufficiently recovered, and the voltage difference between the Purkinje and ventricular plateaus was relatively small. At longer intervals, however, recovery of transient outward current dictated a larger difference between the Purkinje and ventricular plateaus, which resulted in the flow of significant electrotonic current and shortening of both action potential durations. Relative cell mass is also likely to affect restitution during heterogeneous coupling as well.

V. Conclusion

Restitution importantly defines rate-dependent changes in action potential duration that may contribute to the onset of tachycardia from a premature beat and the transition from tachycardia to fibrillation [6]. The Purkinje-ventricular interface may be particularly susceptible to these arrhythmias because Purkinje and ventricular cells have different restitution kinetics, and many antiarrhythmics differentially alter action potential duration in Purkinje and ventricular cells. Because electrotonic coupling additionally modulates action potential duration, this study has implications for the proarrhythmic effects of some antiarrhythmic drugs.

Acknowledgment

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